REMARKS

Claims

The subject matter of new Claim 44 is fully supported in the present application as filed July 19, 2001. Support can be found in the specification, for example, at page 5, line 3, which incorporates by reference the entire contents of U.S. Patent Nos. 5,500,412 and 5,352,664; in the two paragraphs added at page 6, line 16, between paragraph 1 and paragraph 2 (see the Reply to Restriction Requirement and Preliminary Amendment, filed December 6, 2002); and at page 7, lines 8-10. No new matter has been added by the new claim.

An "-NH_2" appearing at the C-terminus of SEQ ID NO.: 6 indicates that SEQ ID NO.: 6 is amidated at its C-terminus.

Sequence Listing

Transmitted concurrently herewith is a copy of a Substitute "Sequence Listing" in paper form (sheets 1/3 through 3/3) comprising SEQ ID NOs.:1-6 for the above-identified patent application as required by 37 C.F.R. §§ 1.825(a) and 1.821(c), and a copy of the Substitute "Sequence Listing" in computer readable form as required by 37 C.F.R. §§ 1.825(b) and 1.821(e). Please replace the "Sequence Listing" filed on December 6, 2002 (sheets 1/3 through 3/3) with the Substitute "Sequence Listing" filed concurrently herewith.

The Substitute Sequence Listing filed concurrently herewith correctly recites that SEQ ID NO.: 5 consists of the 23 amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val. Support for this correction to the sequence listing is found in the specification, for example, at page 7, lines 8-10.

The Substitute Sequence Listing filed concurrently herewith also correctly recites that SEQ ID NO.: 6 consists of the 23 amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val. Support for this correction to the sequence listing is found in the amended specification, for example, at page 7, lines 19-22, where it is stated that SEQ ID NO.: 6 has the identical amino acid sequence of SEQ ID NO.: 5 and also contains a *C*-terminal amide.

As required by 37 C.F.R. § 1.825(b), Applicants' Attorney hereby states that the contents of the Substitute "Sequence Listing" in paper form and in the computer readable form submitted concurrently herewith are the same and, as required by 37 C.F.R. § 1.825(a), also states that the submission includes no new matter.

Rejection of Claims 1-5, 11-16 and 35-43 Under 35 U.S.C. § 112, First Paragraph

Claims 1-5, 11-16 and 35-43 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not provide enablement for the use of "any agonist of non-proteolytically activated thrombin receptor, any thrombin peptide derivative or physiologically functional equivalent thereof" in the claimed methods of stimulating bone growth at a site in a subject in need of osteoinduction or bone grafting. Paper No. 10, at page 5, lines 2-7. Applicants respectfully disagree with this assessment.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02. The Federal Circuit has held that "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." Gould v. Quigg, 3 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987) (*quoting* In re Chilowsky, 108 U.S.P.Q. 321, 325 (C.C.P.A. 1956)).

The Federal Circuit has also stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. . . . However, experimenation needed to practice the invention must not be undue experimentation." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the sate of the art. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Id.

A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The specification teaches that NPAR agonists are osteoinductive and thus, can stimulate bone growth at a site within a subject at which bone growth would not occur if the site were left untreated. The specification teaches that, as a result, NPAR agonists can be used in stimulating bone growth at a site in a subject where osteoinduction is needed (see, e.g., page 2, line 23 to page 3, line 6).

The specification teaches that NPAR agonists are compounds which stimulate or activate NPAR (see, e.g., page 4, lines 17-19). Methods for assaying for NPAR activation are disclosed in the specification (see, e.g., page 4, line 28 to page 5, line 4). Methods for assaying for NPAR activation are also disclosed in U.S. Patent No. 5,352,664 ('664) and U.S. Patent No. 5,500,412 ('412), which are incorporated by reference in the subject application. Methods for identifying and screening for NPAR agonists and methods for producing NPAR agonists are disclosed in the specification (see, e.g., page 8, line 27 to page 9, line 3; and page 14, line 22 to page 15, line 3) and in the '664 and '412 patents. Examples of NPAR agonists are provided in the specification, for example, at page 6, line 1 to page 9, line 7. Specific examples of NPAR agonists provided in the specification include thrombin peptide derivatives comprising a polypeptide represented by the structural formula Asp-Ala-R, wherein R is a serine esterase conserved sequence, such as the thrombin peptide derivative of SEQ ID NO.: 5 and SEQ ID NO.: 6 (see, e.g., page 6, line 1 to page 7, line 20). Other specific examples of NPAR agonists are provided in the '664 and '412 patents. Thus, armed with Applicants' teachings in the specification and what was known to the skilled artisan at the time the subject application was filed, it would be a routine matter to identify and produce NPAR agonists for use in the claimed methods.

Applicants have exemplified the effects of NPAR agonists using the NPAR agonist TP508. In particular, Applicants have demonstrated that an injury resulting in a segmented gap

did not heal when it was left untreated; bone regeneration (osteoinduction) did not occur at the segmented gap. However, when the site was treated with TP508, bone mineralization and growth (osteoinduction) was induced where it did not occur without TP508. See, e.g., Example 2, pages 17-19. Accordingly, Applicants have demonstrated that TP508 is osteoinductive and induces bone formation in sites where bone formation did not occur without TP508 treatment.

Thus, since the NPAR agonist TP508 has been shown to be osteoinductive, stimulating bone formation in sites where bone formation would not occur with TP508 treatment, one skilled in the art would reasonably expect that other NPAR agonists can be successfully employed to stimulate bone formation at a site where bone formation would not occur if the site was left untreated. That is, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence has been provided as to why the results achieved using TP508 cannot be correlated to other NPAR agonists.

In addition, in the Rule 132 Declaration of Darrell H. Carney, Ph.D., filed concurrently herewith, data are disclosed showing that osteoblasts have high-affinity thrombin receptors and respond to NPAR agonists such as TP508, resulting in stimulation of osteoblast proliferation. These data provide further evidence that one skilled in the art would expect that other NPAR agonists can be successfully employed to stimulate bone formation at a site where bone formation would not occur if the site was left untreated.

Moreover, the '664 and '412 patents set forth results which demonstrated that epithelial cells and fibroblast cells have high-affinity thrombin receptors and that NPAR agonists, including TP508, can bind specifically to the thrombin receptors. These U.S. earlier patents also disclose results which demonstrate that NPAR agonists acting on thrombin receptors, can induce DNA synthesis and promote epithelial cell proliferation. These results demonstrate that NPAR agonists, such as TP508, are effective in promoting significant biological responses.

In addition, the claims of the '664 and '412 patents recite analogs of TP508. Thus, in issuing the '664 and '412 patents, the USPTO has confirmed the effects of this broader range of NPAR agonists. The USPTO relied primarily on data for TP508 in issuing the '664 and '412 patents with claims reciting a broader range of NPAR agonists. Therefore, claims at least as

broad with respect to TP508 analogs in the '664 and '412 patents should be allowable in the present application.

Accordingly, as explained by Dr. Carney in the Declaration, since activation of NPAR causes osteoblasts to proliferate, NPAR agonists other than TP508, e.g., those which act on epithelial and fibroblast cells, are also expected to cause osteoblast proliferation. NPAR agonists other than TP508 are also expected to be osteoinductive and stimulate bone formation in sites where bone formation would not occur without treatment, given the evidence in the subject application. In particular, analogs of TP508 such as those recited in claims of the '664 and '412 patents are expected to stimulate osteoblast proliferation, and be osteoinductive, stimulating bone formation at sites where osteoinduction is needed (i.e., at sites where bone formation would not occur if the sites were left untreated).

Accordingly, the specification provides enablement for the full scope of Claims 1-5, 11-16 and 35-43.

Claims 1-5, 11-16 and 35-43 have also been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. In particular, the Examiner alleges that "[w]ith the exception of SEQ ID NO:5 and SEQ ID NO:6, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." Paper No. 10, at page 7, lines 15-18. Applicants respectfully disagree with this assessment.

To fulfill the written description requirement, a patent specification must describe the claimed invention in sufficient detail that a person skilled in the art can reasonably conclude that Applicants were in possession of the claimed invention at the time the present application was filed. Vas-Cath, Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Written description may be satisfied through disclosure of relevant identifying characteristics, i.e., structure, other physical and/or chemical characteristics, of the claimed subject matter sufficient to distinguish it from other material. University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d

1398, 1404 (Fed. Cir. 1997). If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., Vas-Cath at 1116; Martin v. Johnson, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972).

Applicants provide detailed characteristics for the NPAR agonists recited in the rejected claims (i.e., Claims 1-5, 11-16 and 35-43). In particular, Applicants' specification teaches that NPAR agonists are compounds which stimulate or activate NPAR (see, e.g., page 4, lines 17-19). Methods for assaying for NPAR activation are disclosed in the specification (see, e.g., page 4, line 28 to page 5, line 4). Methods for assaying for NPAR activation are also disclosed in the '664 and '412 patents, which are incorporated by reference in the subject application. Examples of NPAR agonists are provided in the specification, for example, at page 6, line 1 to page 9, line 7. Specific examples of NPAR agonists provided in the specification include thrombin peptide derivatives comprising a polypeptide represented by the structural formula Asp-Ala-R, wherein R is a serine esterase conserved sequence (see, e.g., page 6, line 1 to page 7, line 20).

Other specific examples of NPAR agonists are provided in the '664 and '412 patents. Methods for identifying and screening for NPAR agonists and methods for producing NPAR agonists are disclosed in the specification (see, e.g., page 8, line 27 to page 9, line 3; and page 14, line 22 to page 15, line 3) and in the '664 and '412 patents. Thus, it is evident that the knowledge and level of skill in this field is high. As such, a person skilled in the art would recognize from the disclosed characteristics that Applicants were in possession of the claimed genus of NPAR agonists at the time the present application was filed.

The Written Description Guidelines provides that where the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. See Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description Requirement, published in the Federal Register, Volume 66, Number 4, at page 1106 (January 5, 2001). Accordingly, the specification sufficiently describes the subject matter of Claims 1-5, 11-16 and 35-43 and Applicants have satisfied the written description requirement.

Reconsideration and withdrawal of the rejection of Claims 1-5, 11-16 and 35-43 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claims 5, 11, 12 and 35-43 Under 35 U.S.C. § 112, Second Paragraph

Claims 5, 11, 12 and 35-43 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Each aspect of this rejection is discussed below.

Firstly, Claim 5 has been rejected to as indefinite on the grounds that the claim recites both closed ("consists") and open ("between about 12 and about 23") language.

Applicants respectfully disagree that recitation of both the term "consists" and the phrase "between about 12 and about 23" renders Claim 5 indefinite. The test for definiteness is whether one skilled in the art would understand the metes and bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987).

Applicants' specification teaches numerous NPAR agonists consisting of between about 12 and about 23 amino acids. Thus, although the term "about" provides flexibility to the lower and upper ends of the recited range of amino acids, the skilled artisan would readily understand what is claimed, in light of the specification. As such, Claim 5 is definite and the metes and bounds are clear, when read in light of Applicants' specification.

Secondly, Claims 11 and 12 have been rejected to as indefinite on the grounds that they depend on claims drawn to a non-elected group.

As suggested by the Examiner, Claims 11 and 12 have been amended to depend on elected Claim 4, thereby obviating this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

Thirdly, Claims 11, 12 and 35-43 have been rejected to as indefinite on the grounds that "it is unclear what sequences are being claimed".

As indicated above, the sequence listing has been corrected to recite that SEQ ID NO.: 5 and SEQ ID NO.: 6 consist of the 23 amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-

Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val, thereby obviating this aspect of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-5, 11, 12, 16 and 35-37 Under 35 U.S.C. § 102(b)

Claims 1-5, 11, 12, 16 and 35-37 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Simmons *et al.* (*Calcium Metabolism: Comparative Endocrinology*, International Satellite Symposium, 2nd, San Francisco, CA, November 30, 1998).

Applicants respectfully disagree with the Examiner's conclusion that Claims 1-5, 11, 12, 16 and 35-37 are anticipated by the teachings of Simmons *et al.* The Court of Appeals for the Federal Circuit has stated that "[u]nder 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference." Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986) (citations omitted).

Claims 1-5, 11, 12, 16 and 35-37 relate to the use of NPAR agonists, including TP508 (SEQ ID NO.:5), in stimulating bone growth at a site in need of osteoinduction or in need of a bone graft. "Osteoinduction" is defined in the subject application at page 3, lines 19-20 as a site at which bone growth would not occur if the site were left untreated. Such sites in need of osteoinduction include segmental bone gaps, bone voids and at non-union fractures. The healing process (bone regeneration) at such a site does not occur without osteoinduction or bone grafting.

Indeed, in Example 2, Applicants demonstrated that an injury resulting in a segmented gap did not heal when it was left untreated; bone regeneration (osteoinduction) did not occur at the segmented gap. **However, when the site was treated with TP508, bone mineralization and growth (osteoinduction) was induced where it did not occur without TP508.** See specification, Example 2, pages 17-19.

In contrast, Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the progression of rat femoral fracture healing. Healing of this fracture (bone regeneration) was occurring prior to TP508 treatment, indicating that treatment (including bone grafting and osteoinduction) **was not required for normal bone growth**. Thus, Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the rate of *normal* fracture healing in a fracture that normally heals without treatment. Simmons *et al.* do not teach or suggest the use of TP508 for stimulating bone formation at site in need of osteoinduction or bone

grafting, i.e., at a site where bone growth would not occur if the site was left untreated. As such, Claims 1-5, 11, 12, 16 and 35-37 are not anticipated by the Simmons *et al.* reference.

Reconsideration and withdrawal of this rejection of Claims 1-5, 11, 12, 16 and 35-37 under 35 U.S.C. § 102(b) are respectively requested.

Rejection of Claims 13-15 Under 35 U.S.C. § 103(a)

Claims 13-15 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Simmons *et al.* in view of Schmitz (U.S. Patent No. 4,637,931).

Teachings of the Cited References

Simmons *et al.*

Simmons *et al.* is discussed above. In summary, Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the rate of *normal* fracture healing in a fracture that normally heals without treatment. Simmons *et al.* do not teach or suggest that TP508 is osteoinductive. As such, Simmons *et al.* do not teach or suggest, with a reasonable expectation of success, that TP508 can be used in stimulating bone formation at a site in need of osteoinduction (i.e., at a site where bone growth would not occur if the site was left untreated).

Schmitz

Schmitz is cited by the Examiner as teaching "a method comprising implanting at the site of the broken osseous tissue a therapeutically effective amount of a composition comprising decalcified freeze dried bone incorporated into a biodegradable polymeric matrix of PLA/PGA". Paper No. 10, at page 10, lines 19-22. Schmitz is also cited by the Examiner as teaching that "the copolymer-decalcified freeze dried bone implant material is successful at stimulating bone repair" and "may be osteoinductive". Paper No. 10, at page 10, lines 22-25

However, Schmitz does not teach or suggest the use of pharmaceutical compositions comprising an NPAR agonist, such as TP508 (SEQ ID NO.:5), in stimulating bone growth at a site in need of osteoinduction. As such, the Schmitz patent does not cure the deficiencies of the Simmons *et al.* reference.

Combination of References

In support of the rejection, the Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art "to modify the teachings of Simmons *et al.* and Schmitz to make the instant invention of a method for stimulating bone growth at a site comprising administering in a pharmaceutical composition an agonist of non proteolytically activated thrombin receptor and an implantable biocompatible carrier". Paper No. 10, at page 11, lines 1-5. The Examiner alleges that one of ordinary skill in the art would be motivated to do so because "Simmons *et al.* teach a way to heal bone fractures using TP508 which avoids the risk of over stimulating target cells" and "Schmitz teaches the use of suitable carriers comprising matrices which induce migration of bone progenitor cells at sites of fractures". Paper No. 10, at page 11, lines 5-10.

Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Moreover, it appears that the Examiner has used Applicants' specification as an instruction manual or template to piece together the proposed combination of references in an attempt to establish a *prima facie* case of obviousness. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Notwithstanding the above, a *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

Neither of the cited references (Simmons *et al.*, Schmitz), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention

was made with a reasonable expectation of success. More specifically, neither of the cited references, alone or in combination, would have suggested the use of a NPAR agonist in a method of stimulating bone growth at a site in a subject in need of osteoinduction or bone grafting, with a reasonable expectation of success. As discussed above, Simmons *et al.* teach that TP508 can be used in enhancing the mechanical strength and accelerating the rate of *normal* fracture healing in a fracture that normally heals without treatment. Schmitz teaches the use of a bone repair material consisting of decalcified freeze-dried bone and biodegradable biodegradable, biocompatible copolymer for improving and accelerating the healing of osseous tissue. Importantly, neither references teaches or suggests that NPAR agonists, including TP508, are osteoinductive or that NPAR agonists can stimulate bone growth at a site within a subject at which bone growth would not occur if the site were left untreated, i.e., at a site in need of osteoinduction or bone grafting. In fact, prior to Applicants' results described in the subject application, one of ordinary skill in the art would not have reasonably expected NPAR agonists to be osteoinductive.

Reconsideration and withdrawal of the rejection Claims 13-15 under 35 U.S.C. § 103(a) are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) was filed on July 25, 2003. Entry and consideration of the IDS are respectfully requested.

Request For Interview

Applicants respectfully request a telephonic interview with the Examiner prior to issuance of the next Office Action.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If

the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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